

REMARKS

I. Status Summary

Claims 1-6, 8-13 and 29-30 are pending in the present application and are presently examined. The U.S. Patent and Trademark Office (hereinafter "the Patent Office") has rejoined claims 8-14 which had been previously withdrawn. Claims 17-27 are withdrawn from prosecution at this time. Claims 1, 8, 10 and 12 are amended herein. Claims 7, 14 and 28 have been canceled.

The specification has been objected to for the presence of an embedded hyperlink and typographical error and claim 14 is objected to for allegedly being a substantial duplicate of claim 8. Claim 1 is rejected under 35 USC § 112, second paragraph. Claims 1-6, 8-14 and 29-30 are rejected under 35 USC § 101. Claims 1-6 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Jelinsky et al. (*Mol. Cell Biol.*, Vol. 20, No. 21, pp. 8157-67, November 2000; hereinafter "Jelinsky et al.") in view of U.S. Patent Application Publication No. 2004/0009479 to Wohlgemuth et al. (hereinafter "Wohlgemuth et al."). Claims 8-14 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Jelinsky et al. in view of Wohlgemuth et al. in further view of U.S. Patent No. 5,830,645 to Pinkel et al. (hereinafter "Pinkel et al.").

II. Claim Amendments

Claim 1 is amended to replace the term "its" at line 5 with the phrase "each oligo probe's". Claim 1 is further amended at the last line to recite: "wherein the corrected oligo probe hybridization signals are outputted to a computer memory". Support for these amendments can be found throughout the claims and specification as filed and, in particular, at page 2, lines 7-8; at page 3, lines 29-34; and at Figures 1, 2 and 4. Accordingly, no impermissible new matter has been added by this claim amendment.

Claim 8 is amended at line 4 by insertion of the term "the" to clarify that the gDNA recited in line 4 refers to the gDNA previously recited in line 3. Claim 8 is

further amended at line 6 to replace the term "different" with the phrase "the multiple" to clarify that the hybridizations recited in line 6 refer to those previously recited in line 4. Claim 8 is further amended by addition of a new step at line 7 reciting: "calculating an average signal for each probe from the normalized signal intensities". Support for this amendment can be found throughout the claims and specification as filed and, in particular, at original claim 9 and Figures 1, 2 and 4. Claim 8 is further amended at line 9 by addition of the phrase "by requiring the signal average to be equal to a constant". Support for this amendment can be found throughout the claims and specification as filed and, in particular, at original claim 10 and Figures 1, 2 and 4. Claim 8 is further amended at the end to recite: "wherein the correction coefficients are outputted to a computer memory". Support for this amendment can be found throughout the claims and specification as filed and, in particular, at page 3, lines 29-34. Accordingly, no impermissible new matter has been added by these claim amendments.

Claim 10 is amended by deletion of language directed to calculation of correction coefficients based on requiring a signal average to be equal to a constant and insertion of language reciting: "comprising determining an uncertainty coefficient for each oligo probe". Support for this amendment can be found throughout the claims and specification as filed and, in particular, at original claims 8 and 11 and Figures 1, 2 and 4. Accordingly, no impermissible new matter has been added by these claim amendments.

Claim 12 is amended by changing the dependency from claim 8 to claim 10 to achieve consistency with the foregoing amendments.

III. Response to Objections to Specification

The specification has been amended as indicated by the amendment above to delete the embedded hyperlink and to correct the typographical error. No new matter has been added. In view of the above amendments, applicants respectfully request withdrawal of the objections to the specification.

IV. Response to Objections to the Claims

The Patent Office has objected to claim 14 as being a substantial duplicate of claim 8. Claim 14 is herein canceled. Accordingly, the objection is obviated by amendment.

V. Response to the Rejections under 35 U.S.C. § 112, Second Paragraph

Claim 1 is rejected under 35 USC § 112, second paragraph, as allegedly being indefinite for use of the term "its" at line 5. Applicants respectfully disagree with the § 112, second paragraph, rejection and respectfully assert that claim 1 is not unclear. However, in order to facilitate prosecution of the application, claim 1 is herein amended as suggested by the Examiner to recite "each oligo probe's" in place of "its". Accordingly, present claim 1 is clear and Applicants thus respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

VI. Response to the Rejections under 35 U.S.C. § 101

Claims 1-6, 8-14 and 29-30 are rejected under 35 USC § 101 as allegedly failing to recite a tangible step. While Applicants respectfully disagree with the § 101 rejection, in order to facilitate prosecution of the application, the claims are herein amended as suggested by the Examiner. Independent claims 1 and 8 are amended at the end to recite, respectively: "wherein the corrected oligo probe hybridization signals are outputted to a computer memory" and "wherein the correction coefficients are outputted to a computer memory". Accordingly, present claims 1-6, 8-14 and 29-30 recite a tangible result, and Applicants thus respectfully request withdrawal of the rejection under 35 U.S.C. § 101.

VII. Response to the Rejections Under 35 U.S.C. § 103(a)

Claims 1-6 have been rejected under 35 USC § 103(a) as allegedly being unpatentable over Jelinsky et al. (*Mol. Cell Biol.*, Vol. 20, No. 21, pp. 8157-67,

November 2000; hereinafter "Jelinsky et al.") in view of U.S. Patent Application Publication No. 2004/0009479 to Wohlgemuth et al. (hereinafter "Wohlgemuth et al."). In addition, claims 8-14 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Jelinsky et al. in view of Wohlgemuth et al. in further view of U.S. Patent No. 5,830,645 to Pinkel et al. (hereinafter "Pinkel et al."). Applicants respectfully traverse the rejections under § 103(a).

In response to the 35 U.S.C. §103(a) rejections, applicants respectfully submit the attached Declaration under 37 CFR §1.131 regarding Wohlgemuth et al. Summarily, the attached Declaration establishes that the inventive subject matter of claims 1-6 and 8-14 was invented prior to April 11, 2001, which is earlier than the priority date of June 8, 2001 claimed by Wohlgemuth et al. Consequently, it is respectfully submitted that the rejection of claims 1-6 and 8-14 under 35 U.S.C. §103(a) as being obvious in view of Wohlgemuth et al. as part of the cited combination has now been rendered moot. It is therefore respectfully requested that Wohlgemuth et al. as a reference be withdrawn, and hence, that the rejection of claims 1-6 and 8-13 under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In light of the above amendments, remarks and the enclosed 131 affidavit, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Application Serial No.: 10/500,587

DEPOSIT ACCOUNT

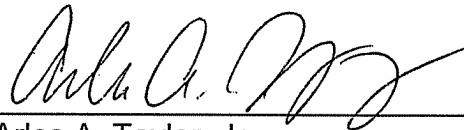
The Commissioner is hereby authorized to charge any additional fees associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: March 7, 2008

By:



Arles A. Taylor, Jr.

Registration No. 39,395

1392/10/21 PCT/US

AAT/LLK/dbp

Customer No: 25297

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Zou et al.

Group Art Unit: 1631

Serial No.: 10/500,587

Examiner: Karlheinz R. Skowronek

Filed: June 30, 2004

Docket No.: 1392/10/21 PCT/US

Confirmation No.: 5250

For: PROBE CORRECTION FOR GENE EXPRESSION LEVEL DETECTION

* * * * *

DECLARATION PURSUANT TO 37 C.F.R. § 1.131

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313/1450

Sir:

1. We, Guangzhou Zou, Hur-Song Chang, Yiping Fan, Fan Long, Xun Wang and Tong Zhu are co-inventors of the invention disclosed and claimed in the subject above captioned U.S. Patent Application Serial No. 10/500,587 filed October 21, 2004, which claims priority to PCT Application No. PCT/US03/01636 filed January 17, 2003, which claims priority to U.S. Provisional Application Serial No. 60/349,874 filed January 18, 2002.
2. We have had the opportunity to review the Official Action mailed on December 7, 2006, and the Official Action mailed on September 7, 2007, from the U.S. Patent and Trademark Office for the subject above captioned U.S. Patent Application Serial No. 10/500,587.

Serial No. 10/500,587

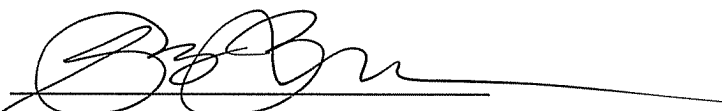
3. We have also reviewed the following documents cited by the United States Patent and Trademark Office in the Official Actions mailed on December 7, 2006, and September 7, 2007, respectively:
 - (a) Journal article by Tseng et al. published in *Nucleic Acids Research*, 2001, Vol. 29, No. 12, pp. 2549-2557 (hereinafter 'Tseng'). Upon information and belief, the date of acceptance of this article for publication is April 10, 2001, and, therefore, the date of publication of this article is no earlier than April 10, 2001; and
 - (b) U.S. Patent Application Publication No. 2004/0009479 by Wohlgemuth et al. published on January 15, 2004 (hereinafter 'Wohlgemuth'). Upon information and belief, the priority date of this publication is June 8, 2001.
4. We have had the opportunity to review claims 1-6, 8-13 and 29-30 of the subject above captioned U.S. Patent Application Serial No. 10/500,587, and the subject matter embodied in claims 1-6, 8-13 and 29-30 was invented prior to the April 10, 2001 acceptance date of the Tseng article and, therefore, also prior to the June 8, 2001 priority date of the Wohlgemuth publication.
5. Attached hereto are a true and accurate hard copy of an electronic version of an Invention Disclosure Form (**Exhibit A**) and true and accurate hard copies of associated electronic attachments titled "gscale.ppt" (**Exhibit B**) and "application.doc" (**Exhibit C**), which were submitted to the Intellectual Property Department of the former Torrey Mesa Research Institute (hereinafter 'TMRI'). Exhibits A, B and C document the subject matter embodied in pending claims 1-6, 8-13 and 29-30 of the subject above captioned U.S. Patent Application Serial No. 10/500,587. This submission of Exhibits A, B and C was made prior to April 10, 2001. Upon information and belief, at the time of the conception and reduction to practice of the subject matter described in pending claims 1-6, 8-13 and 29-30 of the subject patent application, TMRI was owned by

Serial No. 10/500,587

Syngenta Participations AG, the assignee of the subject above captioned U.S. Patent Application Serial No. 10/500,587. Exhibits A, B and C are believed to provide evidence of the subject matter recited in the pending claims, which predates the acceptance date of the Tseng article and the priority date of the Wohlgemuth publication.

I hereby declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 2-12-2008

By: 
Guangzhou Zou

Date: _____

By: _____
Hur-Song Chang

Date: _____

By: _____
Yiping Fan

Date: _____

By: _____
Fan Long

Date: _____

By: _____
Xun Wang

Date: _____

By: _____
Tong Zhu

Serial No. 10/500,587

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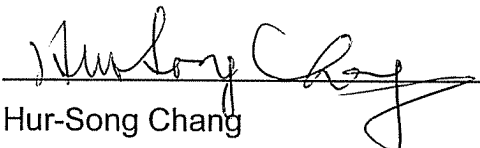
I hereby declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: _____

By: _____

Guangzhou Zou

Date: Feb. 13, 2008

By: 

Hur-Song Chang

Date: _____

By: _____

Yiping Fan

Date: _____

By: _____

Fan Long

Date: _____

By: _____

Xun Wang

Date: _____

By: _____

Tong Zhu

Serial No. 10/500,587

Syngenta Participations AG, the assignee of the subject above captioned U.S. Patent Application Serial No. 10/500,587. Exhibits A, B and C are believed to provide evidence of the subject matter recited in the pending claims, which predates the acceptance date of the Tseng article and the priority date of the Wohlgemuth publication.

I hereby declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: _____

By: _____

Guangzhou Zou

Date: _____

By: _____

Hur-Song Chang

Date: _____

By: _____

Yiping Fan

Date: _____

By: _____


Fan Long

Date: _____

By: _____

Xun Wang

Date: 1/12/2008

By: 

Tong Zhu

TMRI Invention Disclosure Form

PREFACE

An Invention Disclosure (“ID”) should be submitted when a researcher believes that he or she has conceived or developed something new and useful, or obtained unusual, unexpected, or non-obvious research results.

The purpose of an ID is: 1) to enable a determination by the Intellectual Property Department and management on whether your invention is patentable and/or commercially feasible, and 2) to confirm or establish a conception date. This ID form has been designed to serve such purpose.

Please note, however, that this form is not intended to solicit all of the important and useful information for drafting a robust patent application. Should TMRI decide on patenting your invention, it is likely that you will be requested to provide additional information and/or materials for preparing a patent application that would support claims having significant scope.

In deciding when to submit an ID, please consider the following rules and explanations:

1. Disclose first, publish later.

Submitting an ID of an invention would not adversely impact any subsequent publication of the same. Conversely, publishing an invention without an earlier ID submission and obtaining an attendant review of the ID likely will adversely impact any effort to patent or commercialize the invention.

2. Disclose as soon as the invention is clearly, concretely and completely conceptualized, and no later.

You should not delay submitting an ID of an invention until it has been reduced to practice (i.e., completing one or more embodiments of the invention). An ID should be submitted as soon as you have conceived a definite and complete invention. There is, however, no advantage to submitting disclosures of **vague, abstract or incomplete** ideas. Such ideas are neither patentable nor commercially useful.

3. Leave procedural and patentability questions to the appropriate offices.

What constitutes a patentable invention, and who are inventors under the patent laws, are complex legal questions to be decided solely by patent attorneys. Further, patenting is not the only or necessarily the best means for advancing or protecting TMRI’s interests. Thus,

whether a patentable invention should be patented is a strategic decision requiring inputs from various offices within the company.

INSTRUCTIONS

Please complete each and every section with a clear, detailed and thorough response. Where a section is not applicable, please so indicate. **Use additional sheets or attach drawings or illustrations as necessary**, and make specific reference to such sheets and illustrations in your response.

Submit an **ELECTRONIC COPY** and a **SIGNED PAPER COPY** of the completed form to the Intellectual Property Department (Tim Torchia, Rm 266, x1067, timothy.torchia@syngenta.com).

The Intellectual Property Department will provide you a memo confirming receipt of your ID form and assigning an ID number for tracking purpose.

1. TITLE OF INVENTION.

Correction of oligo probes for the gene expression level detection with genomic-DNA.

2. ABSTRACT OF THE INVENTION. (Please limit to one paragraph.)

Synthesized oligos are often used as probes to detect gene expression levels through hybridization. However, due to sequence-dependent binding constants, the measured expression levels are also probe dependent. The measured values are comparable only when they are from similar probes. Thus, we cannot compare expression level between different genes, for example, can not compare values obtain by different technologies, and cannot relate the measurements to any biological meaningful concepts such as the number of copies per cell. The disclosed method provides a solution to these problems. It will also increase the accuracy of the measured data and eliminate the cross-hybridization signal to a certain degree. Thus, the method can greatly increase the value of all oligo-based gene expression technologies.

3. DESCRIPTION OF THE INVENTION. (Please provide **clear, detailed and complete** descriptions of the following: 1. the essence of your invention [i.e., the critical elements, steps and/or properties of the invention]; 2. all possible aspects of your invention [e.g., a novel gene construct invention includes additional aspects such as the nucleotide sequence, encoded protein, transformed cells containing the construct, and various uses of the foregoing]; 3. various important embodiments of the invention [e.g., the various embodiments of an inducible gene construct would include the different types of promoters that could be used in the construct]; 4. optional elements that could be included in the invention [e.g., a gene construct could optionally comprise a transcription termination signal]. Use additional sheets or attach drawings or illustrations as necessary.)

see attachment: gscale.ppt

3. DESCRIPTION OF THE INVENTION CONTINUED.

4. APPLICATIONS OF THE INVENTION. (Please describe obvious and potential [be creative] applications of the invention.)

see attached: gscale.ppt and application.doc

5. ADVANTAGES OF THE INVENTION OVER EXISTING TECHNOLOGY.

(Please describe how the invention solves existing unsolved problem(s), or improves upon and/or provides an alternative to existing technology.)

see attachment: application.doc

6. RELEVANT PRIOR ART. (Please list all publications including but not limited to patents, applications, publications, and bulletins disclosing material closely related to subject matter of the invention. Attach results of any search that has been done. You may be requested to provide copies of listed publications).

7. LIST PAST OR EXPECTED DATE OF PUBLICATION OR PUBLIC DISCLOSURE OF YOUR INVENTION.

<u>EVENT OR JOURNAL</u>	<u>SUBMISSION DATE</u>	<u>PUBLICATION OR PRESENTATION</u>
<u>DATE</u>		

8. CONTRACT IDENTIFICATION. (Please identify any support material received from outside of TMRI related to the research from which the invention resulted. List any and all Material Transfer, Research, License, and Confidentiality Agreements that may be relevant).

9. IDENTIFICATION OF CONTRIBUTORS. (Please list all internal and external collaborators of project(s) leading to the invention and/or within which the invention was made.)

Guangzhou Zou TMRI

Xun Wang TMRI

Tong Zhu TMRI

Fan Long TMRI

Hur-song Chang TMRI

10. NOTEBOOKS/RECORDS THAT DOCUMENT THE CONCEPTION AND/OR DILIGENCE TO REDUCING THE INVENTION TO PRACTICE.

(Please specifically identify all relevant documents, records and/or Emails, and their date of entry.)



GRNAD a good name
.msg



TMRI Microarray
Proposal 59 - Approv

SIGNATURES:

DATE: _____
(PERSON SUBMITTING THIS DISCLOSURE)

(TYPE OR PRINT NAME)

DATE: _____
(SUPERVISOR or WITNESS)

(TYPE OR PRINT NAME)

**

TO BE COMPLETED BY INTELLECTUAL PROPERTY DEPARTMENT

DISCUSSED WITH INVENTOR ON _____
BY _____

☐ MEMO SENT

☐ DATABASE ENTRY

☐ FILE

DOCKET NUMBER _____

☐ SEARCH

☐ HOLD

Number: _____

☐ PRIOR ART SEARCH

☐ PRIORITIZATION REQUIRED
Code: _____

Cost Center: _____ **Account**

☐ PRIORITY 1 2 3

☐ RELEVANT LICENSE AGREEMENT: _____

☐ OUTSIDE COUNSEL ASSIGNED _____

☐ TMRI MANAGEMENT: HIGH PRIORITY

☐ TMRI MANAGEMENT: LOW PRIORITY

☐ SYNGENTA OPTION DECISION REQUESTED ON _____

☐ SYNGENTA OPTION DECISION DEADLINE BY _____

☐ SYNGENTA OPTION DECISION RESULT: _____

Part I: Obtaining Correction Coefficients

Determine the dynamic range for gDNA binding by measuring the concentration-signal curve

Measure the signals from each oligo during multiple hybridizations with gDNA within the linear range

Normalize the signal intensities from different hybridizations either globally or locally depending on the technologies.

Calculate the average and standard deviation (or similar statistical measures) for the hybridization signals observed on each oligo

Calculate the correction coefficient for each oligo by requiring its signal average equals to a constant (i.e. 1),

$$c_i = \frac{1}{s_i}$$

where s_i is the average of the signals observed on probe 'i'.

Calculate an uncertainty coefficient for each oligo as the ratio between the average and the standard deviation ,

$$d_i = \frac{\bar{s}_i}{\sigma_i}$$

or other similar statistical measure, where σ_i is the standard deviation of signals observed on oligo 'i'

Consider to redesign or disregard the probe if its uncertainty coefficient is greater than 1.0.

Part II: Use of Correction Coefficients

Calculate the corrected signal value on a probe. The corrected signal for a probe can be calculated as

$$S_i^{corrected} = c_i S_i$$

where S is the observed signal on probe i .

Calculate the weighting factor for a probe. If m (≥ 1) oligos are used to detect the expression level of one gene, the weighting factor for the i th oligo can be calculated as:

$$w_i = \frac{d_i}{\sum_l^m d_l}$$

where d is the uncertainty coefficient. In the case where only one oligo is used to represent a gene ($m=1$), then the weighting factor w equals to 1.0.

Calculate the expression level for a gene. The weighting factor can be used to calculate the expression value for a gene. For example, in the simplest case, the expression of a gene can be calculated as:

$$v = \frac{1}{m} \sum_{i=1}^m w_i S_i^{corrected}$$

where v is the expression value and m is the number of the probes used to detect the gene.

Calculate the uncertainty of the gene expression level D :

$$D = \frac{1}{m} \sum_{i=1}^m d_i S_i^{corrected}$$

Convert the corrected signal to the number of copy per cell. In the case when the number of copy per cell value is known for one gene, we can convert the measurements of all other genes to the number of copy per cell values. Let n_0 be the number of copies per cell for gene 0. If n_0 is known, we can obtain the number of copies per cell value for any other gene α as:

$$n_\alpha = \frac{S_\alpha^{corrected}}{S_0^{corrected}} n_0$$

The value will thus become technology independent.

Correction of oligo probes for gene expression level detection with genomic-DNA

Guangzhou Zou, Ph.D

Principal Scientist
Fan Long

Bioinformatics Scientist
Tong Zhu, Ph.D.

Principal Scientist
Xun Wang, Ph.D.
Director, RNA Dynamics

Torrey Mesa Research Institute
3115 Merryfield Row
San Diego, CA 92121

Gene expression analysis is becoming mainstream in post-sequence era. In the past year, more than 7 million independent gene expression measurements have been made at NADI alone. However, there are serious obstacles to accurately mining and systematically integrating the data. Fundamentally, how to compare the expression levels between different genes, how to determine the absolute expression values, and how to eliminate the cross-hybridization signals?

Here, we propose to re-scale and correct each individual probe on micro-arrays with a set of probe dependent coefficients derived from genomic-DNA hybridization signals. The genomic-DNA re-scaled and corrected data will have following advantages:

- (1) It will be more accurate. Rescale these probe measurements by genomic-DNA signal could correct/reduce the errors due to the variable hybridization constant from probe to probe. The error estimation, average signal calculation, and other statistical analysis will be more meaningful and relevant to the expression levels.
- (2) Comparing the expression of different genes will become possible, The correction coefficient rescale the binding affinity of all probes to the same scale by gDNA signals. If the binding constant of DNA is proportional to that of RNA, signals from any probe will become comparable even when RNA is actually used in the hybridization experiments.
- (3) It will potentially become an inter-operable standard among different technologies. Since comparison between different genes becomes possible, the corrected data from a particular technology could be easily converted to copies per cell through some type of controlled signals and become independent to the technology itself.

- (4) It could eliminate the cross-hybridization signal to a certain degree. If we model the hybridization and cross-hybridization on a probe 'i' as following,

$$p = aS_o - b_i(1 - p). \quad (1)$$

where p is the percentage of the total transcript pool, a is a constant, b_i is probe-dependent coefficient reflecting cross-hybridization signal, and S_o is observed signal strength. The above model can be rewritten as follows:

$$p = \left(a - \frac{b_i(1 - p)}{S_o} \right) S_o \approx \left(a - \frac{b_i(1 - p)}{p/a} \right) S_o \approx a(1 - Nb_i)S_o \quad (2)$$

where N is the total copies of the RNA in the pool and is presumed to be much larger than the copies from any single gene. The result (2) corresponds to the first-order approximation of the model (1). It indicates that the cross-hybridization effects can be roughly represented by a set of probe-dependent coefficients.

Due to the high usage of the micro-array data in discovery and development researches, we consider this study very important and urgent. It could have profound impact to the gene expression data mining and results interpretation. In order to represent signals from the entire dynamic range of a particular micro-array and eliminate any noise due to unknown factor, we propose to use up to 10 rice chips for the hybridizations with variable g-DNA concentrations.